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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,654	11/05/2001	Gotz Nowak	ALBRE17	5284

23599 7590 02/27/2004

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EXAMINER	
SAUCIER, SANDRA E	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 02/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,654	NOWAK ET AL.	
	Examiner	Art Unit	
	Sandra Saucier	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-18* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,12 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10, 12-18 are pending. Claims 9, 10, 12, 14-18 are considered on the merits. Claims 1-8 and 13 are withdrawn from consideration as being drawn to a non-elected invention.

Election/Restriction

This application contains claims drawn to an invention nonelected with traverse in Paper No. 4/9/03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

Claims 14, 16 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims now include a standard curve in the kit; however, no standard curve was included in the kits disclosed in the specification or original claims. Contrary to the inserted new matter requiring the inclusion of a standard curve, the instruction is given in the working example to replace the standard sample which is used to generate the standard curve with the unknown. That is, the instruction seems to be to generate a standard curve in each laboratory for each putative inhibitor and use it to determine the concentration of each inhibitor. The standard curve would reasonably be expected to be distinct for each distinct inhibitor as the degree of inhibition of coagulation per mass/volume of each inhibitor would be distinct. For example, a gram/l of hirudin would not be expected to have the same inhibitory value as a gram/l of EDTA or heparin. Further, no Fig. 1 (the standard curve) appears in the as-filed specification. There is only a mention of a non-existent Figure 1 in the example.

Claim Rejections - 35 USC § 102

Claims 9, 10 and 12 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by Han *et al.* [AU].

The claims are directed to a kit comprising:
1) a solution of a coagulation-inhibiting substance not interfering in the transformation of prothrombin into active meizothrombin or meizothrombin fragment 1,

2) a chromogenic or fluorogenic substance dissociable by active meizothrombin or meizothrombin fragment 1,

3) a solution of a substance dissociating prothrombin into meizothrombin or meizothrombin fragment 1

Claim 12 further has a solution of prothrombin.

The references are relied upon as explained below.

Han *et al.* disclose components comprising 1) antithrombin, 2) tosyl-Gly-Pro-Arg-p-nitroanilide and 3) factors Xa, Va and phospholipid. They are used in a test of inhibition of prothrombin activation products by antithrombin (Fig. 4). Thus, these chemicals have been assembled in the prior art for a similar purpose, that is, the testing of the inhibition of the coagulation process by a thrombin inhibitor.

Insofar as the composition claims rely on the inclusion of components which instead of being characterized by technical features suitable for the identification of components which are compounds, is imprecisely defined by means of functional features which merely recite the desired result to be achieved, the subject matter is considered to be anticipated by the disclosure of the prior art.

Applicants' arguments filed 12/12/03 have been fully considered but they are not persuasive.

Applicants argue that Han *et al.* do not disclose the usefulness of the chemical compounds for measuring unknown inhibitor concentrations. While this may be true, the claims are directed to an assemblage of compounds not to a method of using them. Applicants further argue that Han *et al.* do not disclose a single test kit package comprising a standard curve. This is true and no claims comprising a standard curve are rejected over this reference.

Claim Rejections - 35 USC § 103

Claims 9, 10, 12, 15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,547,850 [AA] in view of US 5,702,912 [A] or Houbouyan *et al.* [U].

The claims are directed to a kit comprising:

1) a solution of a coagulation-inhibiting substance not interfering in the transformation of prothrombin into active meizothrombin or meizothrombin fragment 1, such as heparin,

2) a chromogenic or fluorogenic substance dissociable by active meizothrombin or meizothrombin fragment 1, such as a p-nitroanilide type substrate,

3) a solution of a substance dissociating prothrombin into meizothrombin or meizothrombin fragment 1, such as ecarin,

or the direct substitution of 3) by meizothrombin or meizothrombin-des fragment 1.

Claim 12 is directed to the inclusion of a separate solution of prothrombin as another component in the test kit.

US 5,547,850 discloses a composition comprising:

1) heparin,
2)
3) ecarin,
4) meizothrombin and/or meizothrombin-des-fragment 1 (col. 2, l. 26-33).

The composition is used for the determination of hirudin and other thrombin inhibitors.

The composition lacks (2) the chromogenic substrate which produces p-nitroanilide for spectrographic analysis and the inclusion of a separate vial of prothrombin.

The detection of the end point of the reaction is performed with an electrically triggered coagulation test (col. 3, l. 39). This test is also known as the ecarin clotting time test.

US 5,702,912 discloses an assay for determining the concentration of inhibitors of thrombin where the assay for the activity of thrombin may be either a coagulation (clotting) test or a chromogenic substrate for thrombin such as S2238 (Kabi) which is read spectroscopically (col. 5, l. 61-67). The reagents are:

1) clotting factor reagent comprising prothrombin, antithrombin III,

2) chromogenic substrate for thrombin (S2238) and EDTA and

3) activator

Houbouyan *et al.* disclose the equivalency of the chromogenic method of detection (amidolytic method) which is read spectroscopically and the clotting end point for the determination of the concentration of thrombin inhibitors

present in a sample. Both measure thrombin activity. The chromogenic substrate is S2238 which releases p-nitroanilide for spectroscopic analysis at 405nm.

The substitution of the chromogenic assay for the clotting assay in the method of '850 would have been obvious when taken with '912 or Houbouyan *et al.* who disclose the equivalency of such a substitution for the determination of thrombin activity. Therefore, the addition of a chromogenic substrate to the composition of '850 in order to detect the activity of thrombin spectroscopically in a chromogenic assay instead of a clotting end point would have been obvious.

The addition of an individual solution of prothrombin to the kit would have been obvious as it may be used with hiruden or analogs of hiruden to generate standard curves in non-plasma samples which may not have sufficient native prothrombin concentrations for performance of the assay or it may be used for the generation of the meizothrombin or meizothrombin-des-fragment 1 with ecarin for use in the assay.

Applicants' arguments filed 12/12/03 have been fully considered but they are not persuasive.

Applicants argue that the method described in the '850 patent is based on a different principle in which the delay in coagulation is used as a measure of inhibition. While the end point used to determine thrombin inhibitor concentration in a fluid is certainly based on a different principle, the interchangeability of the clotting end point for the chromogenic end point is a choice of the practitioner. Both of these types of end point measurement for thrombin inhibitors is known in the art as evidence by the cited art.

Applicants further argue that there is no motivation to substitute a chromogenic/fluorogenic substance in the clotting method of '850 with a reasonable expectation of success.

The motivation flows from the cited reference of '912 or Houbouyan *et al.* which both teach the equivalency of a clotting end point type assay or the use of a chromogenic method as the end point of the assay for the determination of inhibitors of thrombin. One of skill in the art, given these direct teaching of equivalency, would reasonably expect success from the substitution of a clotting end point for a chromogenic end point in the determination of the concentration of thrombin inhibitors (see Houbouyan *et al.* abstract).

One of skill in the art may detect the activity of thrombin in any manner known in the art for the performance of an ecarin-mediated, thrombin inhibitor test as suggested by the references with a reasonable expectation of success.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (703) 308-1084. The examiner can normally be reached on Monday, Tuesday, Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (703) 308-4742. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sandra Saucier
Primary Examiner
Art Unit 1651